administration containing complexes of cationic liposomes constituted of phospholipids and polydeoxyribonucleotides having a molecular weight in the range 15,000-60,000 Da, said polydeoxyribonucleotides obtained by depolymerization of nucleic acids, in the complexes the polydeoxyribonucleotides being located on the outer surface of the liposomes.

C1 cancelled.

REMARKS

Claims 1-12 and 19-22 were rejected. Claim 1 is amended. Support for the amendment can found throughout the application, for instance in the claims as originally filed. Applicants emphasize that the amendments of claim 1 including the amendment of molecular weight range are not made in view of any claim rejection or prior art, but merely to more clearly set forth the present invention. No new matter is added. Claims 1-12 and 19-22 are submitted for further consideration at this time. Applicants respectfully request reconsideration and withdrawal of all rejections.

Claim Rejections - 35 U.S.C. 103

Claims 1-12 and 19-22 were rejected under 35 U.S.C. 103(a) as being obvious over certain alleged statements of prior art in combination with Litzinger itself or in further combination with Maccarone and/or Eastman. It is alleged in the Office Action that the use of cationic liposomes for the delivery of polynucleotides known in the art would have been

obvious since the prior art shows that oligonucleotides are able to efficiently transfect when complexed with cationic liposomes.

Applicants respectfully disagree. Applicants respectfully submit that those of ordinary skill in the art viewing the cited disclosure and references would have no motivation to combine the teachings of such disclosure and references in an attempt to yield the claimed invention. Since the efficient transfection of oligonucleotides is cited in the Office Action as motivation to combine certain teachings of the prior art, Applicants point out that the term "transfection" means the transfer of genetic material from donor to recipient (See page 144 of Glossary of Biotechnological Terms) (attached). However, Applicants emphasize that the polydeoxyribonucleotides for use in complexes of cationic liposomes as claimed are obtained by depolymerization of deoxyribonucleic acids (See page 6, lines 10-14 of specification). Applicants thus point out that the polydeoxyribonucleotides as claimed have no known transfection activity. As an example of a polydeoxyribonucleotide of the claimed invention, Applicants point to defibrotide (See page 4, lines 3-4 of the specification) which is known to have no transfection activity, as is demonstrated by the document PROCICLIDE -Summary of Product Characteristics/Technical Data Sheet for Scientific Information ("PROCICLIDE Summary") (attached). The PROCICLIDE Summary in particular indicates that in connection with PROCICLIDE, "no mutagenic effects [are] observed" (See para. 5.3 of PROCICLIDE Summary). PROCICLIDE is of course a trade name for pharmaceutical preparations containing defibrotide (See para. 5.1 of PROCICLIDE Summary).

Applicants therefore submit that polydeoxyribonucleotides obtained by depolymerization of nucleic acids as claimed necessarily lack mutagenic properties, that is, the ability to transfer genetic material from donor to recipient. Accordingly, the cited disclosure and Litzinger, Maccarone and Eastman references, with their alleged teachings of efficient transfection, are unable to teach or suggest the claimed invention including polydeoxyribonucleotides that necessarily lack mutagenic properties. Applicants urge that those of ordinary skill in the art viewing the prior art are provided with no teaching or suggestion that polydeoxyribonucleotides obtained by depolymerization of deoxyribonucleic acids, that is, polydeoxyribonucleotides lacking transfection activity, are able to provide for enhanced therapeutic properties when complexed with liposomes. Indeed, with reference to the statements of Eastman that the plasmid DNA used therein brings about inflammation when administered to experimental animals (See page 766, last two periods in left column, of Eastman), Applicants note the substantial differences between the polydeoxyribonucleotides of the claimed invention as compared to the deoxyribonucleic acids of the prior art. Applicants point out that such inflammation effects are quite the opposite of the anti-inflammatory effects and anti-inflammation therapy produced when administering polydeoxyribonucleotides obtained by depolymerization of deoxyribonucleic acids, as claimed (See page 4, lines 11-12 of the Specification). The cited disclosure and references simply do not contain any teaching or suggestion regarding the use of liposomes for enhancing pharmacological activities of polydeoxyribonucleotides as claimed, that is, polydeoxyribonucleotides obtained by

depolymerization of nucleic acids and having a molecular weight in the range of 15,000-60,000 Da. In sum, the polydeoxyribonucleotides obtained by depolymerization of nucleic acids in the claimed invention are provided with an absence of transfection activity, and therefore, those of ordinary skill in the art would have no motivation to combiner or modify any teachings of the prior art in an attempt to yield the claimed invention.

Applicants also note that it is alleged in the Office Action that the stability of polynucleotides in complex form is to be expected rather than unexpected. Applicants respectfully but strongly disagree. Applicants understand that the enhanced pharmacological activity of polydeoxyribonucleotides is known to those of ordinary skill in the art. With reference to the paper of Gursoy et al., the specification at page 3, lines 5-14 indicates that it is known that complexes of liposomes with polydeoxyribonucleotides obtained by depolymerization of nucleic acids show remarkable increases in pharmacological activity. Gursoy discloses a complex of liposomes encapsulating defibrotide, that is, a polydeoxyribonucleotide obtained by depolymerization of deoxyribonucleic acids. Also, in commenting on pharmacological experiments regarding anti-inflammatory activity, Gursoy indicates that such activity significantly increases when defibrotide is encapsulated in the liposome. However, it is to be noted that in later experiments as set forth in this application, Applicants were able to demonstrate that these liposome complexes are indeed not stable and that the enhanced anti-inflammatory activity decreases quickly with time. Accordingly, before the claimed invention, it was not possible for those of ordinary skill in the art to prepare pharmaceutical formulations so as to exploit

therapeutic advantages as provided by such liposome complexes. That is, stability for polydeoxyribonucleotides obtained by depolymerization of nucleic acids as claimed, was not to be expected, as is aptly demonstrated by the experimental data regarding stability over time of liposome complexes as found in the prior art. In view of such unexpected results as to stability, Applicants respectfully urge that the prior art including the cited disclosure and references cannot be considered to teach or suggest the claimed invention.

Applicants further note the certain references, for instance Eastman and Zelphati, are cited in the Office Action as providing additional support for the rejection of the claimed invention. However, Applicants point to the Eastman reference, with reference to Figure 1C and page 768 (top right column), where it is indicated that after 40 minutes, less than 10% of the plasmid DNA complexed to cationic lipid was degraded. In other words, Eastman also recognizes the instability of the liposome complex, that is, after 40 minutes the stability of the liposome complex was no more 100%. Although it is alleged in the Office Action that the abstract of Zelphati refers to enhancing the stability of oligonucleotides by cationic liposomes, Applicants point out that Zelphati simply indicates that cationic liposomes are able to protect oligonucleotides from nuclease degradation. This disclosure of Zelphati adds nothing more to the knowledge in the prior art as compared to the Gursoy reference, which also discloses the preparation of cationic liposome complexes of polydeoxyribonucleotides. Gursoy discloses that liposomes of polydeoxyribonucleotides *in vivo* pharmacological activity models are more effective than polydeoxyribonucleotides, and thus, such liposome complexes might protect

polydeoxyribonucleotides from nuclease degradation. However, like the other cited disclosure and references, Zelphati provides no teaching, suggestion or motivation regarding liposomes of polydeoxyribonucleotides obtained by depolymerization of nucleic acids, in accordance with the claimed invention, much less such liposomes of polydeoxyribonucleotides for addressing the problems of stability as found in the prior art. Applicants urge withdrawal of all rejections.

In light of the discussion above, Applicants respectfully urge that the claimed invention is in condition for allowance and request early notification to that effect.

In the event this paper is not timely filed, Applicants hereby petition for an appropriate extension of time. The fee for this extension may be charged to our Deposit Account No. 01-2300, along with any other additional fees which may be required with respect to this paper.

Please charge any fee deficiency or credit any overpayment to Deposit Account No. 01-2300.

Respectfully submitted,

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Enclosure: Glossary of Biotechnology Terms, page 144
PROCICLIDE - Summary of Product Characteristics/Technical Data Sheet for Scientific Information

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Claim 1 (Amended). A stable pharmaceutical formulation [suitable] for [providing by] parenteral administration [a therapeutically effective amount of polydeoxyribonucleotides to a patient, the pharmaceutical formulation comprising] containing complexes [formed by] of cationic liposomes constituted of phospholipids and polydeoxyribonucleotides having a molecular weight in the range [7,000-60,000 Da] 15,000-60,000 Da, said polydeoxyribonucleotides obtained by depolymerization of nucleic acids, [wherein] in the complexes the polydeoxyribonucleotides [are] being located on the outer surface of the liposomes.